DOCKET NO: ISIS0055-100 (RTS-0236) **PATENT**

REMARKS

Claims 1, 2, 4-15, 20-24, and 26-40 were pending in the present application. Claim 1 has been amended herein and claims 20-24, 26-28, 30, and 32-40 have been cancelled herein. Upon entry of the present amendment, claims 1, 2, 4-15, 29, and 31 will remain pending. No new matter has been added. **Because the amendments to the claims remove issues for appeal (*i.e.*, anticipation), Applicants respectfully request that they be entered into the record. See, M.P.E.P. § 714.12.**

I. The Claimed Invention Is Novel and Not Obvious

A. The Koesters Reference

Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. §102(b) and §103(a) as allegedly anticipated by and/or obvious over Koesters *et al.*, *Genomics*, **1999**, *61*, 210-218 (hereinafter the "Koesters reference"). According to the Office Action, the Koesters reference reports compounds that would specifically hybridize and inhibit the expression of EIF2C1 because the compounds are 100% identical to the target sequence and, without countervailing evidence, it is assumed that the compounds would inhibit the expression of EIF2C1. Applicants traverse the rejection and respectfully request reconsideration of the same in view of amended claim 1.

Although Applicants respectfully disagree with the assumption regarding activity, solely to advance prosecution, Applicants have amended claim 1 to recite that the compounds are "modified," support for which can be found at, for example, page 2, lines 2-13 of the specification. As the Office is well aware, for a reference to be anticipating it must teach every limitation recited in the claims. There is nothing in the Koesters reference that teaches or suggests that the primers reported therein should be modified in any manner. Indeed, the primers reported in the Koesters reference were used *in vitro* for cloning and PCR. One skilled in the art would not have been motivated to modify the primers of the Koesters reference in the manner recited in Applicants' claims.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(b) and/or §103(a) be withdrawn.

B. The Schalling Reference

Claims 1, 2, 12 and 14 are rejected under 35 U.S.C. §102(c) and §103(a) as allegedly anticipated and/or obvious by U.S. Patent No. 5,695,933 (hereinafter, the "Schalling reference"). According to the Office Action, the Schalling reference reports compounds that would specifically hybridize and inhibit the expression of EIF2C1 because the compounds are 100% identical to the target sequence and, without countervailing evidence, it is assumed that the compounds would inhibit the expression of EIF2C1. Applicants traverse the rejection and respectfully request reconsideration of the same in view of amended claim 1.

Although Applicants respectfully disagree with the assumption regarding activity, solely to advance prosecution, Applicants have amended claim 1 to recite that the compounds are "modified," support for which can be found at, for example, page 2, lines 2-13 of the specification. As the Office is well aware, for a reference to be anticipating it must teach every limitation recited in the claims. There is nothing in the Schalling reference that teaches or suggests that the primers reported therein should be modified in any manner. Indeed, the primer reported in the Schalling reference was used as a target because it was an expanded repeat. One skilled in the art would not have been motivated to modify the primer of the Schalling reference in the manner recited in Applicants' claims.

In view of the foregoing, Applicants respectfully request that the rejection under 35 U.S.C. § 102(e) and/or §103(a) be withdrawn.

II. The Claimed Invention Is Not Obvious

Claims 1, 2, 4-15, 20, 24, and 28-31 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over the Koesters reference in view of Cikaluk *et al.*, *Mol. Biol. Cell*, **1999**, *10*, 3357-3372 (hereinafter the "Cikaluk reference"), Taylor *et al.*, *Drug Discovery Today*, **1999**, *4*, 562-567 (hereinafter the "Taylor reference"), U.S. Patent No. 5,801,154 (hereinafter the "Baracchini reference"), and Milner *et al.*, *Nature Biotechnology*, **1997**, *15*, 537-540 (hereinafter the "Milner reference"). Applicants traverse the rejection and respectfully request reconsideration thereof.

In establishing a *prima facie* case of obviousness under 35 U.S.C. §103, it is incumbent upon the Examiner to provide a reason why one of ordinary skill in the art would have been led to modify a prior art reference or to combine reference teachings to arrive at the claimed invention. *Ex parte Clapp*, 227 U.S.P.Q. 972 (Bd. Pat. App. Int. 1985). To this end, the requisite motivation must stem from some teaching, suggestion or inference in the prior art as a whole or from the knowledge generally available to one of ordinary skill in the art and not from appellants' disclosure, see for example, *Uniroyal Inc. v. Rudkin-Wiley Corp.*, 5 U.S.P.Q.2d 1434 (Fed. Cir. 1988); and *Ex parte Nesbit*, 25 U.S.P.Q.2d 1817, 1819 (Bd. Pat. App. Int. 1992). In this respect, the following quotation from *Ex parte Levengood*, 28 U.S.P.Q.2d 1300, 1302 (Pat. Off. Bd. App. 1993), is noteworthy:

> Our reviewing courts have often advised the Patent and Trademark Office that it can satisfy the burden of establishing a *prima facie* case of obviousness only by showing some objective teaching in either the prior art, or knowledge generally available to one of ordinary skill in the art, that "would lead" that individual "to combine the relevant teachings of the references." ... Accordingly, an examiner cannot establish obviousness by locating references which describe various aspects of a patent applicant's invention without also providing evidence of the motivating force that would **impel** one skilled in the art **to do what the patent applicant has done**. (citations omitted; emphasis added)

Significantly, the Office Action identifies no "motivating force" that would "impel" persons of ordinary skill to modify the respective teachings of the cited references and achieve the claimed invention.

The Office Action asserts that the Koesters reference reports that human EIF2C1 is an "interesting candidate for potential involvement in Wilms tumorigenesis," referring to page 217 of the Koesters reference (see, page 10 of the Office Action) and, thus, concludes that one skilled in the art would be motivated to inhibit the expression of EIF2C1[1]. Aside from the use of the term "potential" in the cited statement, the Examiner has ignored the sentence that immediately follows the one that was cited. Indeed, the Koesters reference further teaches "However, we have so far been unable to find any evidence of EIF2C1 gene mutations in Wilms tumors (data not

[1] The Koesters reference actually reports "Taken together, these findings could make human EIF2C1 an interesting candidate for potential involvement in Wilms tumorigenesis." (emphasis added).

shown). Thus, at most, the Koesters reference provide a general motivation to further experiment. Applicants do not question the general motivation to further experiment that may be provided in the Koesters reference. This general motivation, however, is not what is required to establish a case of *prima facie* obviousness. Rather, the requisite motivation that must be established is a motivating force that "would impel one skilled in the art to do what the patent applicant has done." Indeed, there are many avenues to take when desiring to modulate the activity of a protein that may be involved in a disease pathway. For example, one skilled in the art may choose to investigate the role of peptides/proteins, antibodies, or even small molecules that may inactivate EIF2C1. The Koesters reference provides no motivation for any particular avenue of research.

The Cikaluk reference reports injection of double-stranded RNA into cells and does not teach or suggest using a compound that is 8 to 50 nucleobases in length (i.e., which is what the Applicants have done). Indeed, the Cikaluk reference is silent as to the size the RNA that is used in its experiments to elucidate the function of GERp95 in *C. elegans*. Thus, the Cikaluk reference provides no motivation to do what Applicants have done. Neither the Koesters nor Cikaluk references provide any motivation to choose any particular avenue to modulate EIF2C1 activity, let alone specifically choose compounds according to claim 1.

What the Office Action appears to suggest is that the claimed invention would have been obvious because it would have been possible to modify EIF2C1 with oligonucleotide compounds. The mere possibility that the prior art can be modified, however, does not itself provide the requisite motivation to do so. *In re Dien*, 152 U.S.P.Q. 550 (C.C.P.A. 1967) (incentive to seek improvement of existing process held to not render change made by applicant obvious, even where the change was one capable of being made from theoretical point of view). The mere possibility for modification and improvement is not the "motivating force" that the Patent Office Board of Appeals and the Federal Circuit have invariably required. If it were, then no modification would ever lack motivation since some change is always possible. Quite to the contrary, an invention is obvious under the patent laws only when the claimed means for effecting an improvement -- as opposed to the possibility of trying any and all means -- is suggested by the prior art. *In re Shaffer*, 108 U.S.P.Q. 326 (C.C.P.A. 1956) (references, viewed by themselves and not in retrospect, must suggest doing what applicant has done). Significantly,

neither of the cited references would have motivated persons of ordinary skill to make the substantial modifications that would have been necessary to produce the claimed invention. It is only with the improper use of hindsight and with the benefit of the Applicants' disclosure that one can discern the desirability of the particular invention now claimed.

Again, the alleged motivation, at most, raises an inappropriate "obvious to try" standard. Indeed, the court made it clear that it is improper to reject claims as "obvious to try" where the motivation to combine references arises merely because the subject matter of the claimed invention is a promising field for experimentation, although the prior art provides only general guidance as to particular form of the claimed invention or how to achieve it. *In re O'Farrell*, 7 U.S.P.Q.2d 1673, 1681 (Fed. Cir. 1988). Without more specific suggestions in the prior art, there is insufficient motivation to combine the cited references. Furthermore, "focusing on the obviousness of substitutions and differences, instead of the invention as a whole, is a legally improper way to simplify the often difficult determination of obviousness." *Gillette Co. v. S.C. Johnson & Son*, 16 U.S.P.Q.2d 1923, 1927 (Fed. Cir. 1990).

In addition to establishing an impelling motivation, to set forth a legally sufficient *prima facie* case of obviousness, the Patent Office must also show that the cited references teach or suggest a claimed invention with a *reasonable expectation of success*. *In re Dow Chemical Co.*, 5 U.S.P.Q.2d 1529, 1531-32 (Fed. Cir. 1988). The Office Action alleges that it would have been *prima facie* obvious at the time the invention was made for one of ordinary skill in the art to design and use antisense molecules for specifically inhibiting EIF2C1 expression because the sequence for EIF2C1 was previously taught by the Koesters reference and because the Taylor, Baracchini, and Milner references provide a reasonable expectation of success.

The Milner reference, however, does not establish a reasonable expectation of success in obtaining compounds that would inhibit EIF2C1 by at least 42%. Indeed, the Milner reference teaches:

> Surprisingly, few oligonucleotides gave significant heteroduplex yield. ... These results help to explain the variable success that is commonly experienced in the choice of antisense oligonucleotides. ... We find no obvious features in the mRNA sequence or the predicted secondary structure that can explain the variation in heteroduplex yield.

(See, Abstract). The Milner reference also teaches:

> Taken with our studies these observations make clear the difficulty of finding good candidates for antisense sequences by methods which are not based on experimental measurements.

(See, page 541, first column). Thus, the Milner reference reinforces the notion that there is no reasonable expectation of success of obtaining active compounds until the experiments are actually carried out. The fact that screening assays are available does not render the claimed invention obvious.

The Office Action appears to conclude that simply because screening assays for evaluating the inhibitory activity of compounds are available and may be routine, one skilled in the art would, thus, have a reasonable expectation of success in obtaining compounds that would inhibit the expression of EIF2C1 by at least 42%. That screening assays are available and routine would only provide a reasonable expectation of success of being able to screen compounds for inhibitory activity. The mere fact that screening assays are available and routine, however, has no bearing on whether one skilled in the art would have a reasonable expectation of success in obtaining compounds that inhibit the expression of a particular gene by a particular amount. The mere availability of an assay infers nothing as to the expected results. Indeed, it is not possible to currently predict the level of inhibition of expression achieved with any particular compound prior to carrying out the appropriate experiments. Applicants submit herewith a Declaration of Dr. Freier, one of skill in the art of oligonucleotide technology. In paragraph 6, Dr. Freier declares that it is not possible to currently predict the level of inhibition of expression achieved with any particular oligomeric compound prior to carrying out the appropriate experiments. In paragraphs 8 and 9, Dr. Freier declares that it is not reasonable to expect for any particular gene or mRNA that oligomeric compounds having at least 42% inhibition in the expression will be obtained. Thus, simply because screening assays are available and may be routine, one skilled in the art would not have a reasonable expectation of success in obtaining compounds that will inhibit the expression of EIF2C1 by at least 42%.

The Taylor reference also does not provide a reasonable expectation of success in obtaining oligonucleotide compounds that would inhibit EIF2C1 by at least 42%. The Office Action asserts that the Taylor reference teaches that "with modern software screening programs

and high affinity chimeras, one of ordinary skill in the art would have to screen only 3-6 oligos in order to generate one that inhibits 66-95%." The Taylor reference, however, is speculative at best. Indeed, the Taylor reference fails to teach the name of this magical software screening program that can deliver such stated results. The Taylor reference also fails to identify the manufacturer of such software screening program. In paragraph 11 of the Declaration, Dr. Freier declares she is not aware of any software screening program that can provide the results stated in the Taylor reference. In addition, Dr. Freier declares in paragraph 11 of the declaration that the Taylor reference does not enable her to practice that which is claimed in the Taylor reference.

The Baracchini reference also does not provide a reasonable expectation of success in obtaining oligonucleotide compounds that would inhibit EIF2C1 by at least 42%. In paragraph 6 of the Declaration, Dr. Freier declares that it is not possible to predict the level of inhibition of expression of a first gene or mRNA with oligomeric compounds that are specific to the first gene or mRNA based upon the results obtained for inhibiting the expression of a **different** gene or mRNA with a **different** set of oligomeric compounds that are specific to the different gene or mRNA. The level of inhibition of expression that is observed for one target, such as the one reported in the Baracchini reference, has no bearing on the level of inhibition of expression expected for a different target.

Therefore, even if one skilled in the art were motivated to combine the cited references in the manner indicated in the Office Action (and Applicants maintain that no such motivation has been established), one skilled in the art would not have had a reasonable expectation of success. In view of the foregoing, Applicant respectfully submits that the Office Action has failed to establish a *prima facie* case of obviousness. In particular, the Office Action has failed to provide any motivation that would **impel** one skilled in the art to modify the cited references so as to produce Applicants' claimed inventions with a reasonable expectation of success. Accordingly, Applicants respectfully request the rejection under 35 U.S.C. §103(a) be withdrawn.